Metabolic functions of the tumor suppressor p53: Implications in normal physiology, metabolic disorders, and cancer

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ABSTRACT

Background: The *TP53* gene is one of the most commonly inactivated tumor suppressors in human cancers. p53 functions during cancer progression have been linked to a variety of transcriptional and non-transcriptional activities that lead to the tight control of cell proliferation, senescence, DNA repair, and cell death. However, converging evidence indicates that p53 also plays a major role in metabolism in both normal and cancer cells.

Scope of review: We provide an overview of the current knowledge on the metabolic activities of wild type (WT) p53 and highlight some of the mechanisms by which p53 contributes to whole body energy homeostasis. We will also pinpoint some evidences suggesting that deregulation of p53-associated metabolic activities leads to human pathologies beyond cancer, including obesity, diabetes, liver, and cardiovascular diseases.

Major conclusions: p53 is activated when cells are metabolically challenged but the origin, duration, and intensity of these stresses will dictate the outcome of the p53 response. p53 plays pivotal roles both upstream and downstream of several key metabolic regulators and is involved in multiple feedback-loops that ensure proper cellular homeostasis. The physiological roles of p53 in metabolism involve complex mechanisms of regulation implicating both cell autonomous effects as well as autocrine loops. However, the mechanisms by which p53 coordinates metabolism at the organismal level remain poorly understood. Perturbations of p53-regulated metabolic activities contribute to various metabolic disorders and are pivotal during cancer progression.

1. INTRODUCTION

p53 is a major tumor suppressor as highlighted by the high prevalence of somatic mutations in *TP53* in many cancer types, and the strong predisposition to multiple early-onset cancers in Li-Fraumeni (LFS) patients that carry germline mutations of *TP53*. Approximately 50% of human tumors harbor *TP53* mutations while the remaining malignancies expressing WT p53 display functional inactivation of the p53 pathway by alternative mechanisms implicating viral oncoproteins or regulators of p53 such as MDM2 or MDM4. p53 acts mainly as a transcription factor that is activated in response to multiple stressors to regulate the expression of genes controlling proliferation and senescence, DNA repair, and cell death [1]. Several laboratories have also highlighted a major role of p53 in metabolism and showed that p53-associated metabolic functions contribute to its tumor suppressive activities [2,3]. Of note, most tumor-associated p53 mutants are missense, encoding a stable form of the protein devoid of its WT transcriptional activities but endowed with novel gain-of-function activities that are not fully understood. Interestingly, some p53 mutants

acquire metabolic functions that contribute to their pro-tumoral activities [4—8]. An additional notion emerging from recent studies relates to the metabolic activities of other key regulators of the p53 pathway but it is currently unclear how the different components of the p53 pathway orchestrate their metabolic activities and by which mechanisms the deregulation of this complex metabolic network contributes to tumorigenesis.

Although the metabolic program that is controlled by p53 at the transcriptional level is becoming clearer, many questions remain unanswered, such as those related to the molecular mechanisms by which metabolic changes signal to p53 and to how p53 controls different subsets of its target genes during metabolic challenges. By integrating multiple input signals that reflect the metabolic status of a cell, p53 behaves as a metabolic sensor and in turn coordinates an adapted metabolic response. The outcome of the p53-driven metabolic response is influenced by the cellular and tissular contexts but the mechanisms underlying the diversity of the metabolic responses regulated by p53 remain poorly understood. Hence, the p53 pathway and metabolism are functionally intertwined, and this has major

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significance not only to cancer progression but also to normal tissue homeostasis and human diseases beyond cancer.

2. P53 CONTROLS MULTIPLE METABOLIC PATHWAYS

Experimental evidence of the multiple roles of p53 in metabolism and their importance in normal tissue function and tumor progression is growing at an impressive rate. While some of these metabolic activities contribute to stress responses during which p53 ultimately leads to cell demise, they are also essential for maintaining cellular homeostasis and guaranteeing cell survival under conditions of non-genotoxic stresses. p53 was initially linked to the control of glycolysis and mitochondrial respiration, but more recent data have highlighted the high connectivity of p53 with multiple metabolic pathways. In this section, we summarize the current knowledge of the complex roles of WT-p53 in metabolism both in normal and cancer cells. We refer the reader to other recent reviews for the description of the metabolic roles of various p53 mutants [4—8] (See Figure 1 and Table 1).

2.1. p53-mediated regulation of glycolysis, the TCA cycle and oxidative phosphorylation

Although p53 promotes glycolysis and inhibits respiration in specialized cells such as pancreatic β-cells or hepatocytes, most data related to p53-associated metabolic activities support the notion that p53 favors oxidative phosphorylation (OXPHOS) over glycolysis in most cell types. Consistent with this notion, p53 deficiency contributes to the metabolic reprogramming of cancer cells towards a more glycolytic profile. p53 functions in glucose uptake involves the transcriptional repression of *SLC2A1/4* that encode the glucose transporters GLUT1/4, or by restricting IKK—NF-κB activation that leads to decreased GLUT3 expression [9,10]. p53 also inhibits glycolysis by regulating the transcription of other genes that directly or indirectly modulate glycolysis including *RRAD*, *PFKFB3/4*, *TIGAR*, and the monocarboxylate transporter 1 (MCT1) -encoding gene *SLC16A1* [11—15]. The role of p53 in this metabolic pathway also involves post-transcriptional mechanisms such as those implicating the regulation of miR-34a, a microRNA that targets several glycolytic enzymes, and
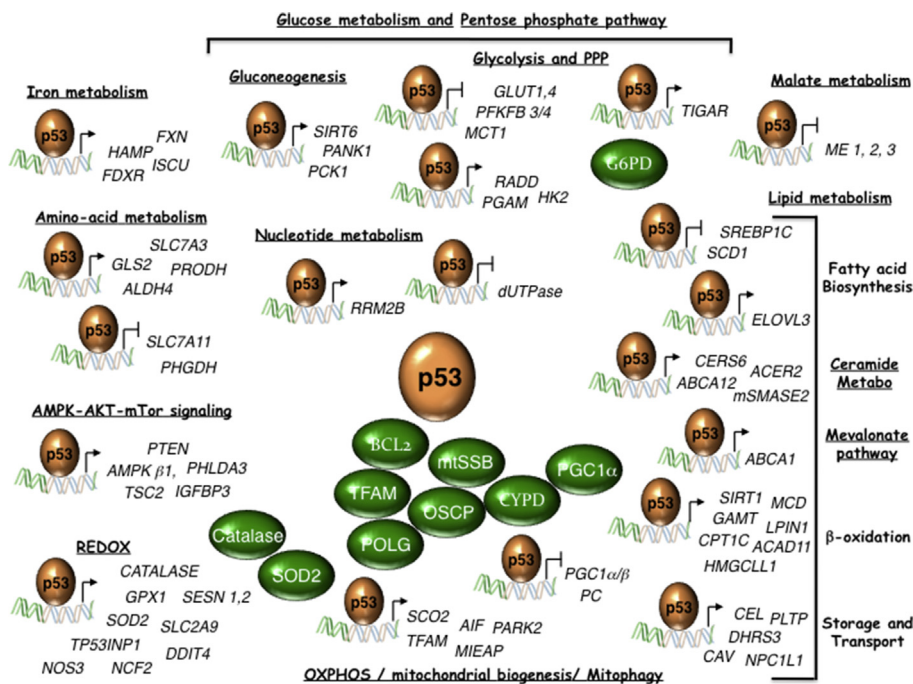

Figure 1: WT-p53 controls multiple metabolic pathways. p53 direct target genes, and p53-interacting proteins (in green) implicated in metabolism are indicated. *ABCA1* (*ATP binding cassette subfamily A member 1*); *ABCA12* (*ATP binding cassette subfamily A member 12*); *ACAD11* (*AcylCoA Dehydrogenase Family member 11*); *ACER2* (*Alkaline ceramidase 2*); *AIF* (*Apoptosis Inducing Factor*); *ALDH4* (*Aldehyde dehydrogenase 4*); *AMPKb1* (*AMP-activated kinase b1 subunit*); BCL2 (B-cell lymphoma 2); *Catalase*; CAV (*Caveolin*); *CEL* (*Carboxy Ester Lipase*); *CERS6* (*Ceramide synthetase 6*); *CPT1C* (*Carnitine Palmitoyl transferase 1C*); CYPD (Cyclophilin D); *DDIT4* (*DNA Damage inducible transcript 4*); *DHRS3* (*Dehydrogenase reductase 3*); *dUTPase* (*deoxyuridine triphosphate nucleotidohydrolase*), *ELOVL3* (*Elongation of very long chain fatty acids-like 3*); *FDXR* (*Ferredoxin Reductase*); *FXN* (*Frataxin*); *GAMT* (*Guanidinoacetate methyltransferase*); *GLS2* (*Glutaminase 2*); *GLUT1* (*Glucose transporter 1*); *GLUT4* (*Glucose transporter 4*); *GPX1* (*Glutathione Peroxidase 1*); *HAMP* (*Hepcidin*); HK2 (Hexokinase II); *HMGCLL1* (*3-hydroxymethyl-3-methylglutaryl-CoA lyase like 1*); mtSSB (Single Stranded DNA Binding protein 1); *IGFBP3* (*IGF-Binding protein 3*); *ISCU* (*Iron-sulfur cluster assembly enzyme*); *LPIN1* (*Lipin 1*); *MCD* (*Malonyl-CoA Decarboxylase*); *MCT1* (*Mono-Carboxylate transporter 1*); *ME1* (*Malic Enzyme 1*); *ME2* (*Malic Enzyme 2*); *ME3* (*Malic Enzyme 3*); MIEAP (*Mitochondria-eating protein*)*; mSMASE2* (*Neutral sphingomyelinase*); *NCF2* (*Neutrophilic cytosolic factor 2*); *NPC1L1* (*Nieman-Pick C1-like* 1); NOS3 (*Nitric Oxide Synthase 3*); OSCP (Oligomycin sensitivity-conferring protein); *PANK1* (*Panthotenate Kinase 1*); *PARK2* (*Parkin*); *PC* (*Pyruvate carboxylase*); *PCK1* (*Phosphoenolpyruvate carboxykinase 1*); *PFKFB4* (*6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 4*); *PFKFB3* (*6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3*); *PGC1α* (*Peroxisome proliferator-activated receptor Gamma, Coactivator 1 alpha*); *PGC1β* (*Peroxisome proliferator-activated receptor Gamma, Coactivator 1 beta*); *PGAM* (*Muscle specific phosphoglycerate mutase*); *PHGDH* (*Phosphoglycerate Dehydrogenase*); *PHLDA3* (*Pleckstrin homology-like domain, Family A, member 3*); *PLTP* (*Phospholipid Transfer Protein*); POLG (*Polymerase γ*); *PRODH* (*Proline Dehydrogenase*); *PTEN* (*Phosphatase and tensin homolog*); *RRAD* (*Ras-related associated with Diabetes*); *RRM2B* (*Ribonucleotide reductase regulatory subunit M2B*); *SCD1* (*Stearoyl-CoA desaturase 1*); *SCO2* (*Synthesis of cytochrome c oxidase 2*); SESN1 (*Sestrin 1*); *SESN2* (*Sestrin 2*); *SIRT1* (*Sirtuin 1*); *SIRT6* (*Sirtuin 6*); *SLC2A9* (*Solute carrier family 2 member 9*); *SLC7A3* (*Solute carrier family 7 member 3*); *SLC7A11* (*Solute carrier family 7 member 11*); *SOD2* (*Superoxide Dismutase 2*); *SREBP1C* (*Sterol regulatory element binding transcription factor 1*); *TFAM* (*Mitochondrial Transcription Factor A*); *TIGAR* (*TP53-induced glycolysis and apoptosis regulator*); *TP53INP1* (*Tumor Protein 53-Induced Nuclear Protein 1*); *TSC2* (*TSC Complex subunit 2*).

Table 1 — P53 direct target genes implicated in metabolism. This table references p53-controlled genes for which experimental evidence supports a direct role of p53 in their transcription.

		Activated/Repressed by p53	Experimental evidences	Bibliography
Nucleotide Synthesis				
dUTPase	Deoxyuridine triphosphate nucleotidohydrolase	repressed	reporter assays, ChIP	[106]
RRM2B/p53R2	Ribonucleotide reductase regulatory/TP53 inducible subunit M2B	activated	ChIP-seq	[107,108,251]
Glucose Metabolism				
Glycolysis and Pentose Phosphate Pathway				
GLUT1	Glucose transporter 1	repressed	reporter assays, EMSA	[9]
GLUT4	Glucose transporter 4	repressed	reporter assays, EMSA	[9]
RRAD	Ras-related associated with Diabetes	repressed	ChIP	[13]
MCT1/SLC16A1	Mono-Carboxylate transporter 1	repressed	ChIP	[11]
M-PGAM	Muscle specific phosphoglycerate mutase	activated	reporter assays, EMSA	[249]
HK2	Hexokinase 2	activated	reporter assays, EMSA, DNAse I Footprint	[250]
TIGAR	TP53-induced glycolysis and apoptosis regulator	activated	ChIP, EMSA, ChIP-seq	[12]
PFKFB4	6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 4	repressed	ChIP	[14]
PFKFB3	6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	repressed	reporter assays, ChIP	[15]
Gluconeogenesis				
PANK1	Panthotenate Kinase 1	activated	ChIP, ChIP-on-ChIP, ChIP-seq, EMSA, reporter assays	[210]
PCK1	Phosphoenolpyruvate carboxylase 1	activated	ChIP	[235]
SIRT6	Sirtuin 6	activated	ChIP	[209]
Lipid metabolism				
Fatty Acid Oxidation				
MCD	Malonyl-CoA Decarboxylase	activated	ChIP-qPCR	[22]
LPIN1	Lipin 1	activated	ChIP-qPCR, ChIP-seq	[23,25,39]
CPT1C	Carnitine Palmitoyl transferase 1C	activated	ChIP-qPCR, ChIP-seq	[24,25,39]
ACAD11	AcylCoA Dehydrogenase Family member 11	activated	ChIP-qPCR, ChIP-seq	[25,39]
HMGCLL1	3-hydroxymethyl-3-methylglutaryl-CoA lyase like 1	activated	ChIP-qPCR, ChIP-seq	[25,39]
Fatty Acid synthesis and storage, lipid transport and lipoprotein metabolism				
SREBP1C	Sterol regulatory element binding transcription factor 1	repressed	reporter assays	[221]
ABCA1	ATP binding cassette subfamily A member 1	activated	ChIP	[45]
NPC1L1	Nieman-Pick C1-like 1	activated	ChIP	[54,235]
SCD1	Stearoyl-CoA desaturase 1	repressed	ChIP-qPCR, ChIP-seq	[49,51]
ELOVL3	Elongation of very long chain fatty acids-like 3	activated	reporter assays, ChIP, EMSA	[224]
ME1	Malic Enzyme 1	repressed	reporter assays, ChIP	[46]
ME2	Malic Enzyme 2	repressed	reporter assays, ChIP	[46]
PLTP	Phospholipid Transfer Protein	activated	reporter assays, ChIP	[54]
CEL	Carboxy Ester Lipase	activated	reporter assays, ChIP, ChIP-seq	[54,251]
CAV	Caveolin	activated	reporter assays, EMSA	[215]
DHRS3	Dehydrogenase reductase 3	activated	reporter assays, EMSA, ChIP	[47,48]
SIRT1	Sirtuin 1	activated/repressed	reporter assays, EMSA, ChIP	[191,192]
CYP19	Aromatase	activated	ChIP	[213]
Sphingolipid metabolism				
CERS6	Ceramide synthetase 6	activated	reporter assays, EMSA	[59]
ACER2	Alkaline ceramidase 2	activated	reporter assays, ChIP-qPCR, ChIP-seq	[54,61,251]
ABCA12	ATP binding cassette subfamily A member 12	activated	ChIP	[60]
nSMANE2	Neutral spingomyelinase	activated	reporter assays	[54]
Amino-acid and ammonia metabolism				
GLS2	Glutaminase 2	activated	ChIP	[20,21,84]
SLC7A3	Solute carrier family 7 member 3	activated	ChIP	[91]
PHGDH	Phosphoglycerate Dehydrogenase	repressed	ChIP, EMSA	[92]
P5CDH/ALDH4	P5C dehydrogenase/Aldehyde dehydrogenase 4	activated	reporter assays, ChIP, EMSA	[95]
PRODH/POX	Proline Dehydrogenase/Proline Oxidase	activated	ChIP, ChIP-PET	[97,98]
CPS1	Carbamoyl phosphate synthetase 1	repressed	reporter assays, ChIP	[102]
OTC	Ornithine transcarbamoylase	repressed	reporter assays, ChIP	[102]
ARG1	Arginase 1	repressed	reporter assays, ChIP	[102]
Mitochondrial Biogenesis, integrity and Respiration				
SCO2	Synthesis of cytochrome c oxidase 2	activated		[26]
TFAM	Mitochondrial Transcription Factor A	activated	reporter assays, ChIP,	[27]
PGC1α	Peroxisome proliferator-activated receptor gamma, coactivator 1 alpha	repressed	ChIP	[195]
AIF	Apoptosis inducing factor	activated	ChIP	[28]
PC	Pyruvate carboxylase	repressed	reporter assays, ChIP	[230]
PARK2	Parkin	activated	reporter assays, ChIP	[40]
MIEAP	Mitochondria-eating protein	activated	reporter assays, ChIP	[41]
Iron Metabolism and Ferroptosis				
Iron Metabolism				
ISCU	Iron-sulfur cluster assembly enzyme	activated	reporter assays, ChIP	[66]
FDXR	Ferredoxin reductase	activated	reporter assays, ChIP, ChIP-seq	[67,68,76,251]

(continued on next page)

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Table 1 — *(continued)*

HAMP	Hepcidin	activated	reporter assays, EMSA, ChIP	[65]
FXN	Frataxin	activated	reporter assays, EMSA, ChIP	[69]
Ferroptosis				
SLC7A11	Solute carrier family 7 member 11	repressed	ChIP-qPCR, EMSA	[79,84]
SAT1	Spermidine/spermine N1-acetyltransferase 1	activated	ChIP-qPCR	[83]
Redox				
SESN1	Sestrin 1	activated	reporter assays, EMSA, ChIP, ChIP-seq	[116,251]
SESN2	Sestrin 2	activated	ChIP-seq	[39,117,251]
ALDH4	Aldehyde dehydrogenase 4	activated	reporter assays, EMSA, ChIP	[95]
GPX1	Glutathione Peroxidase 1	activated	reporter assays, EMSA	[113,252]
SOD2	Manganese dependent superoxide dismutase	activated/repressed	reporter assays, ChIP	[113,125]
CATALASE	Catalase	activated	ChIP	[115]
NCF2/p67phox	Neutrophilic cytosolic factor 2	activated	reporter assays, ChIP	[124]
DDIT4/REDD1	DNA Damage inducible transcript 4	activated	reporter assays	[156]
NOS3	Nitric Oxide Synthase 3	activated	reporter assays, EMSA, ChIP	[203]
TP53INP1	Tumor Protein 53-Induced Nuclear Protein 1	activated	reporter assays, EMSA, ChIP, ChIP-seq,	[120,121,251]
SLC2A9/GLUT9	Solute carrier family 2 member 9	activated	reporter assays, ChIP	[123]
Creatine Biosynthesis				
GAMT	Guanidinoacetate methyltransferase	activated	reporter assays, EMSA, ChIP	[55,96]
Autophagy				
ATG2B	Autophagy related 2B	activated	ChIP-seq	[39]
ATG4A	Autophagy related 4A	activated	ChIP-seq	[39]
ATG4C	Autophagy related 4C	activated	ChIP-seq	[39]
ATG7	Autophagy related 7	activated	ChIP-seq	[39]
ATG10	Autophagy related 10	activated	ChIP-seq	[39]
ULK1	Unc-51 like kinase 1	activated	ChIP-seq, EMSA, reporter assays	[39,139]
ULK2	Unc-51 like kinase 2	activated	ChIP-seq, EMSA, reporter assays	[39,139]
UVRAG	UV radiation resistance associated gene	activated	ChIP-seq	[39]
VMP1/TMEM49	Vacuole membrane protein 1	activated	ChIP-seq	[39]
DAPK1	Death Associated Protein Kinase 1	activated	ChIP, EMSA	[141]
AEN/ISG20L1	Apoptosis enhancing nuclease	activated	ChIP	[138]
DRAM1	DNA damage regulated autophagy modulator 1	activated	reporter assays, ChIP, ChIP-seq	[140,251]
EI24	Etoposide-induced 2.4 kb transcript	activated	ChIP-seq	[251,253]
AMPK, AKT and mTOR signaling				
AMPKβ1	AMP-activated kinase beta 1 subunit	activated	reporter assays, ChIP	[152]
TSC2	TSC Complex subunit 2	activated	reporter assays, ChIP	[152]
PTEN	Phosphatase and tensin homolog	activated	reporter assays, EMSA	[157]
IGFBP3	IGF-Binding protein 3	activated	reporter assays, EMSA	[158]
PHLDA3	Pleckstrin homology-like domain, Family A, member 3	activated	reporter assays, ChIP, ChIP-seq	[159]

the downregulation of the glycolytic enzyme phosphoglycerate mutase (PGM) [16,17].

At the same time, p53 promotes OXPHOS by several complementary mechanisms. First, p53 favors pyruvate oxidation in mitochondria through the down-regulation of the pyruvate dehydrogenase (PDH) kinase PDK2, a negative regulator of the PDH complex (PDC) that converts pyruvate into AcetylCoenzyme A (AcCoA) to sustain the tricarboxylic acid (TCA) cycle [18]. The importance of p53 in fueling the TCA cycle with glucose-derived pyruvate has recently been highlighted in pancreatic cancer models in which restoration of p53 activity was shown to increase α-Ketoglutarate (αKG) levels. By changing the αKG/succinate ratio, p53 loss modulates the activity of αKG-dependent chromatin modifying enzymes, thereby influencing the epigenome of cancer cells and engaging them into a more malignant state [19]. To sustain the TCA cycle, p53 can also concomitantly enhance the flux of several anaplerotic pathways, including glutaminolysis and fatty-acid oxidation (FAO) [20—25]. Moreover, p53 favors mitochondrial respiration by promoting mitochondrial biogenesis, maintaining mitochondrial genome integrity, and enhancing the activity of the electron-transport chain through transcriptional regulation of *Synthesis of Cytochrome c Oxidase 2* (*SCO2*), *Mitochondrial Transcription Factor A* (*TFAM*), *Ferredoxin Reductase* (*FDXR*), and *Apoptosis Inducing Factor* (*AIF*). Beside the regulation of these target genes, p53 also sustains mitochondrial activity through its direct interaction with several mitochondrial proteins that play a key role in mitochondrial genome

replication and repair, including the mitochondrial polymerase gamma (POLG), the human mitochondrial single-stranded DNA-binding protein (HmtSSB), the F_1F_0-ATP synthase subunit OSCP and TFAM [26—33]. Another mechanism by which p53 favors mitochondrial function is through the expression of several components of the mitochondrial protein import machinery, including TOM20, TIM23, mtHSP70, and mtHSP60 [34]. In addition, p53 controls mitochondrial architecture and dynamics. More specifically, p53 supports mitochondrial fission by increasing the expression of the GTPase Dynamin-related protein 1 (DRP1), and by interacting with Prohibitin 1 and subsequent processing of the long form of Opa1 (L-Opa1) that promotes mitochondrial fusion [35—37]. Finally, p53 ensures the quality control and turnover of mitochondria through mitophagy by increasing the expression of Parkin and Mitochondria Eating Protein (MIEAP) [38—41].

2.2. p53 and the Pentose Phosphate Pathway (PPP)

The control of glycolysis by p53 is tightly coordinated with its ability to channel glycolytic intermediates into branched anabolic pathways, among which is the Pentose Phosphate Pathway (PPP). The regulation of the PPP by p53 is important for the production of NADPH to contribute to maintain the redox status by reducing oxidized glutathione, and for the generation of precursors of nucleotide synthesis for DNA repair if cells face DNA damage. However, the role of p53 in the PPP remains ambivalent since several reports suggest that different pools of the p53 protein can either stimulate or repress this metabolic

pathway depending on the cell type and stress conditions. Thus, on the one hand, nuclear p53 controls the efficiency of the glycolytic flux and the channeling of glucose-6-phosphate into the PPP by regulating the transcription of *TIGAR*, *PFKFB3*, and *PFKFB4*, 3 genes encoding enzymes that directly modulate the levels of Fructose-(2,6) bisphosphate (F2,6BP), an allosteric activator of phosphofructokinase 1 (PFK1) [12,14,15]. On the other hand, cytoplasmic p53 inhibits directly the activity of G6P-dehydrogenase (G6PD), the enzyme that controls the first and rate limiting step of the PPP, by preventing the formation of the active dimer [42]. Altogether, these data suggest that the dynamic control of p53 subcellular localization is an important regulatory mechanism of the PPP.

2.3. p53 controls lipid metabolism

Another important aspect of p53 metabolic activities relates to its multiple roles in lipid homeostasis, including in lipid transport and storage, in fatty acid and cholesterol biosynthesis, in sphingolipid metabolism, as well as in FAO [43,44]. At the systemic level, p53 controls the expression of proteins that contribute to complex lipid breakdown and their absorption in the gut (NPC1L1), their transport in the systemic circulation through lipoproteins (PLTP, CEL), and their intracellular flux (ABCA1, ABCA12, CAV). At the cellular level, p53 limits lipid anabolism through convergent mechanisms that decrease de novo fatty acid synthesis and impact the mevalonate pathway, a key metabolic pathway involved in cholesterol and non-sterol isoprenoids biosynthesis. Thus, p53 transcriptionally inhibits *SREBP1c*, a gene encoding the sterol regulatory element-binding protein 1 (SREBP1) transcription factor that activates the transcription of many lipogenic genes. An additional mechanism involves the transcriptional regulation of *ABCA1*, a transporter controlling retrograde cholesterol transport and therefore its abundance in the endoplasmic reticulum (ER), an event regulating SREBP2 maturation and its nuclear translocation [45]. In addition, induction of p53 impinges on lipid synthesis by limiting NADPH production, an essential co-factor for de novo fatty acid synthesis, through the repression of *Malic Enzymes 1* and *2* (*ME1/2*) and, as previously mentioned, by inhibiting the PPP [42,46]. Paradoxically, p53 promotes lipid droplet formation by directly regulating the transcription of *Dehydrogenase reductase 3* (*Dhrs3*), a family member of the short chain alcohol dehydrogenase/reductase superfamily that is important for retinoid metabolism and associates with lipid droplets [47,48]. It is plausible that the regulation of *Dhrs3* by p53 is part of a specialized program that regulates the concentration of cytosolic retinol, and its product retinoic acid, in order to control cell proliferation and differentiation.

Another important aspect of p53 functions relates to its function in fatty acid desaturation. This activity is partly mediated through the transcriptional repression of *Stearoyl-CoA desaturase 1* (*SCD1*), which encodes the enzyme converting saturated to mono-unsaturated fatty acids (MUFAs) [49]. p53-mediated repression of *SCD1* has been documented in several cellular contexts, including in cancer cells in which it impacts membrane phospholipid composition and AKT-signaling, but also in normal fibroblasts engaged in premature senescence, a process during which the abundance of unsaturated fatty acids could change the structure and function of organelles, in particular mitochondria, that play a central role in senescence [50—53].

During nutrient starvation, p53 inhibits fatty acid synthesis and concomitantly enhances lipid catabolism by increasing FAO, a metabolic process that replenishes the pool of mitochondrial AcCoA and provides reducing power (FADH2 and NADH) to support the activity of the electron transport chain. This involves the transcriptional activation

of genes encoding carnitine acyl-transferases that facilitate fatty acids efflux out of the peroxisome (*CROT*) and their transport into the mitochondria (*CPT1A* and *CPT1C*), as well as that of several genes that promote directly or indirectly FAO (*LPIN1*, *ACAD11*, *HMGCLL1*, *GAMT*, *MCD*) [23—25,54,55].

p53 also plays a key function in the metabolism of sphingolipids, a class of lipids that play multiple roles in signaling pathways involved in proliferation, cell death, and differentiation [56]. Indeed, p53 inhibits the expression of sphingosine kinase-1 (SK1), a central enzyme in that metabolic pathway that modulates Sphingosine-1-Phosphate (S1P) levels, through a post-translational mechanism involving cysteine-proteases and the proteasome [57]. The importance of SK1 regulation by p53 during cancer development was confirmed in mice in which genetic inactivation of *Sk1* abrogated lymphomagenesis in *Trp53* knock-out (KO) mice [58]. In addition, in cancer cells, p53 increases the expression of Ceramide synthase 5 (CERS5) and 6 (CERS6) and of the neutral Sphingomyelinase-2 (nSMASE2), three ceramide-generating enzymes, upon DNA damage or folate deprivation [59,60]. These data indicate that p53 can concomitantly increase the synthesis of pro-apoptotic ceramides and decrease the synthesis of the anti-apoptotic S1—P. Paradoxically, p53 also induces the transcription of human *Alkaline ceramidase 2* (*ACER2*) which gene product catalyzes the hydrolysis of ceramides into sphingosine, the precursor of S1P [61]. Finally, it is noteworthy that p53 is part of a feedback loop involving ceramides. Thus, the well-described buildup of ceramides following DNA damage was found to occur in a p53-dependent manner. Interestingly, the massive up-regulation of p53 occurring upon transient induction of CerS6 during serum or folate deprivation results from the direct binding of C_{16}-ceramide to the core DNA Binding Domain of p53 and inhibition of MDM2-mediated degradation by the proteasome [62,63]. Altogether, these studies indicate that p53 is both a target and a modulator of sphingolipid metabolism.

2.4. p53, iron metabolism and ferroptosis

Iron plays a critical role in a variety of biological processes including cell proliferation, and cancer cells display a stronger dependence on iron than do normal cells [64]. Cells utilize free iron (also called labile iron) to synthesize cofactors such as heme and iron sulfur (Fe—S) clusters that are essential for the activity of several enzymes involved in DNA synthesis and repair, as well as those implicated in many oxido—reduction reactions. Iron also functions as a cofactor for lipoxygenases (LOXs). Beyond these essential roles, high iron concentration is deleterious due to the Fenton reaction during which a ferrous iron donates an electron in a reaction with hydrogen peroxide (H_2O_2) to generate a highly reactive hydroxyl radical. Therefore, the uptake, storage, and usage of iron must be tightly controlled and p53 appears to be pivotal in a complex network controlling iron metabolism both at the systemic and the cellular levels by regulating the transcription of several key iron regulators including *Hepcidin* (*HAMP*) [65], *iron-sulfur cluster assembly enzyme* (*ISCU*) [66], *Ferredoxin reductase* (*FDXR*) [67,68], and *Frataxin* (*FXN*) [69]. Different teams have reported that iron chelators, as well as iron overload, lead to p53 stabilization through distinct mechanisms implicating either Hypoxia-Inducible Factor 1 alpha (HIF1α) or MDM2, two direct regulators of p53 which activities are modulated by intracellular iron levels [70—73]. Changes in iron metabolism can also directly impact on p53 transcriptional activities. Thus, the iron polyporphyrin heme was shown to interfere with p53's interaction with DNA, thereby promoting its nuclear export and cytosolic degradation [73]. Finally, ferritin, an iron storage protein, was also reported to bind and activate p53 under oxidative stress [74]. Interestingly, the gene network implicating p53 in iron metabolism

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involves several feedback loops that in turn modulate p53 expression and activity [75]. Thus, *FDXR*, a *bona fide* p53 target gene, encodes a protein that influences p53 translation through a mechanism implicating the binding of the RNA-binding protein IRP2 to the 3′ untranslated region (UTR) region of *p53* mRNA [76]. In neuronal cells and astrocytes, interfering with FXN, that is also regulated by p53 at the transcriptional level, triggers a p53-dependent apoptotic response [77]. It is currently unknown whether modulation of p53 activity by FXN influences the development of the various types of cancer observed in patients suffering Friedreich's ataxia, a rare early-onset degenerative disease linked to FXN deficiency. However, the p53-dependent cell death occuring upon FXN inactivation likely contributes to their neurological symptoms. Altogether, these data illustrate the high connectivity between p53 and iron metabolism and show that perturbations of this network can lead to mitochondrial iron overload, a process associated with tumor predisposition [76].

The importance of p53 in iron metabolism extends to the control of ferroptosis, a non apoptotic cell death mechanism characterized by iron-dependent lipid peroxidation. Interestingly, p53 can promote opposite effects on ferroptosis, through both transcriptional and non-transcriptional mechanisms that are influenced by the cellular context. Several studies indicate that p53 activation promotes ferroptosis and that this function is important for its tumor suppressive activities. The first evidence linking p53 to ferroptosis was identified in genetically engineered mouse models (GEMMs) harboring combined lysine-to-arginine (K→R) mutations located in p53 DNA binding domain. Unexpectedly, knock-in mice expressing a p53 acetylation-defective mutant on K117, K161, and K162 were not cancer prone despite these mutations completely abrogated p53's ability to induce cell cycle arrest, senescence, and cell death in response to acute DNA damage or oncogenic stress. Interestingly, these mutations did not alter the regulation of a subset of p53 metabolic target genes, suggesting that p53 metabolic activities play a key role in tumor suppression *in vivo* [78]. Later, *Slc7a11*, a p53-repressed gene encoding a component of the X_c^- cystine/glutamate antiporter, was identified as an important mediator of p53-associated control of ferroptosis and tumor suppression in this mouse model [79—81]. The lipoxygenase ALOX12, that binds directly to and is inhibited by SLC7A11, was found to be indispensable for p53-mediated ferroptosis [82]. Other p53 metabolic target genes also contribute to its role in ferroptosis, such as *Glutaminase 2* (*GLS2*) that will provide precursors for GSH synthesis (see below), or *SAT1*, which gene product is involved in polyamine catabolism by catalyzing acetylation of spermidine and spermine, a process linked to H_2O_2 production, activation of the ALOX15 lipoxygenase and lipid peroxidation [83]. The role of p53 in sensitizing cells to ferroptosis was confirmed in another GEMM mimicking the p53-S47 genetic variant that is the second most common Single Nucleotide Polymorphism (SNP) within the *TP53* locus found in the human population of African origin. In this animal model, increased cancer predisposition was linked to the inability of the S47-p53 variant to properly regulate some p53 metabolic target genes including *Gls2* and *Slc7a11* [84]. Nevertheless, p53 was also reported to limit or delay ferroptosis in some cancer cells by preventing the relocalisation from the nucleus to the plasma membrane of dipeptidyl-peptidase-4 (DPP4), a positive regulator of ferroptosis, or as a result of p21-mediated cell cycle arrest that contributes to maintain glutathione levels [85,86].

2.5. p53 and amino-acid metabolism

The transcriptional regulation of *GLS2* by p53, which gene product converts glutamine into glutamate and ammonia, was the first evidence linking p53 to amino-acid metabolism. p53-mediated control of

GLS2 contributes to different metabolic pathways and replenishes TCA intermediates when pyruvate oxidation is impaired. It is also important to maintain the redox status of cells by fueling glutathione synthesis [20,21,84]. Although the protective function of p53 during metabolic challenges was initially observed upon glucose starvation [87], it was later extended to conditions where different amino-acids become limiting [88—91]. Consistent with this notion, p53-deficient cells are more sensitive to serine/glycine or glutamine deprivation. In response to glutamine deprivation, p53 drives an adaptive response by inducing the expression of the arginine transporter SLC7A3 that increases temporarily intracellular arginine levels to sustain mTORC1 activity [91], while the induction of the aspartate transporter SLC1A3 supports mitochondrial respiration and nucleotide synthesis [90]. Different components of the p53 pathway are also involved in the cellular response to serine deprivation. Cells facing a limited supply of exogenous serine induce de novo serine synthesis, an anabolic pathway that converts the glycolytic intermediate 3-phosphoglycerate (3 PG) into serine through a multi-step enzymatic process implicating phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1), and phosphoserine phosphatase (PSPH). The link between p53 and serine metabolism was initiallty described by Vousden and colleagues. In serine/glycine-deprived cells, they identified p21 as an important router that constrains the channeling of the remaining pool of serine towards glutathione synthesis at the expense of nucleotide synthesis in order to maintain a proper redox status and to promote cell survival [89]. At the molecular level, p53 and MDM2, independently of each other, have antagonistic roles on the transcriptional control of genes encoding key enzymes involved in serine synthesis. For instance, p53 was reported to repress the *PHGDH* promoter in melanoma cells cultured in complete medium [92], whereas our team more recently reported direct and p53-independent MDM2-mediated activation of *PHGDH*, *PSAT1*, and *PSPH* upon serine/glycine deprivation [93]. In the Ou et al. study, the recruitment of p53 on *PHGDH* promoter was not assessed upon serine—glycine deprivation but only after treatment with the DNA-damaging agent Doxorubicin or Nutlin3A that lead to the full activation of p53. Induction of p53-mediated repression of *PHGDH* by Nutlin3A potentiates cell death in serine/glycine-deprived melanoma cells, suggesting that this combination of treatments impacts on serine/glycine levels synergistically to reach a lethal threshold. It is noteworthy that the cell death induced upon p53 activation by Nutlin3A in these cells depends on ATF4, a transcription factor that is key to recruit MDM2 on the promoter of its metabolic target genes [93]. Therefore, it is plausible that the activities of MDM2, p53, and ATF4 are finely tuned to control the flux through this key metabolic pathway in a biphasic manner. Decreased serine availability may initially promote cell survival through MDM2/ATF4-mediated regulation of serine synthesis and through a p53-p21 axis that maintain the redox balance of these cells. Later, more prolonged or severe depletion of serine/glycine pools (that may ultimately induce to DNA damage) would initiate a vicious cycle during which the repression of *PHGDH* by p53 and the activation of *NOXA* and *PUMA* by ATF4 lead to cell death.

Another pathway involving amino-acids in which p53 plays an important role is proline metabolism. In recent years, proline metabolism has received considerable attention as a mechanism of NAD/NADP regeneration, an anaplerotic source, a potential producer of reactive oxygen species (ROS), and also as a cell signaling hub [94]. p53 induces the transcription of both *Proline dehydrogenase* (*PRODH*)/ *Proline oxidase* (*POX*), initially named PIG6 for "*p53-induced gene 6*", and *Pyrroline-5-Carboxylate* (*P5C*) *dehydrogenase* (*P5CDH*), also referred to as *aldehyde dehydrogenase 4* (*ALDH4*) [95—98]. These two

p53 target genes encode enzymes that catalyze the first and second reactions involved in proline degradation, respectively. PRODH/POX is a mitochondrial enzyme linked to complex II of the electron transport chain (ETC) with a flavine adenine dinucleotide at the active site that transfers electrons to Coenzyme Q. By doing so, proline can serve as an alternative source of energy when glucose and glutamine are limiting, but proline-derived electrons also produce superoxides through complex III, thereby contributing to p53-dependent apoptosis or senescence [96,99,100]. ALDH4 is a NAD^+-dependent enzyme localized in the mitochondrial matrix that catalyzes the second step of proline degradation by converting L-Glutamic-γ-semialdehyde into glutamate. The anti-oxidant effect of ALDH4 has been linked to its ability to exhaust the proline pool [95]. Consistent with its anti-oxidant function, ALDH4 depletion in worms induces the expression of the ROS-sensitive nuclear factor erythroid 2-related factor 2 (NRF2) transcription factor that coordinates proline and fatty acid metabolism [101]. It remains to be determined when p53 preferentially induces ALDH4 over PRODH expression, but the finely tuned regulation of these two enzymes by p53 differentially impacts the redox status of the cells and changes the outcome of p53-mediated responses. Given the metabolic interlock between proline metabolism and the PPP, it is plausible that p53-mediated control of proline metabolism influences some of its multiple effects on the PPP [12,14,15,42]. Finally, proline catabolism is also tightly connected to ureagenesis and polyamines biosynthesis through the conversion of P5C into ornithine, a precursor of polyamines and key intermediate of the urea cycle. Interestingly, p53 has also been shown to influence polyamine biosynthesis through the repression of three key enzymes of the urea cycle, *Carbamoyl phosphate synthetase 1* (*CPS1*), *Ornithine transcarbamoylase* (*OTC*) and *Arginase 1* (*ARG1*). p53 deficiency increases ureagenesis and putrescine levels, thereby promoting proliferation. Moreover, defects in the urea cycle activates p53 in a MDM2-dependent manner, suggesting a positive regulatory loop between p53 and the urea cycle [102]. Thus, while the model remains to be confirmed, p53-coordinated actions on amino-acid catabolism and on the urea cycle might be necessary to regulate polyamine levels.

2.6. p53 and nucleotide synthesis

By inhibiting nucleotide synthesis, p53 limits cell proliferation in unchallenged conditions, but it can also temporarily stimulate metabolic pathways that contribute to both purine and pyrimidine synthesis in response to DNA damage to facilitate DNA repair. Thus, the p53-inducible microRNA-34a (miR-34a) represses inosine 5′-monophosphate dehydrogenase (IMPDH), a rate-limiting enzyme involved in de novo guanosine triphosphate (GTP) biosynthesis [103]. p53 also inhibits guanosine monophosphate (GMP) synthesis by repressing the expression of guanosine 5′-monophosphate synthase (GMPS), one of three glutamine amidotransferases that converts xanthosine 5′-monophosphate (XMP) into GMP [104]. An interesting feedback loop involves p53 and GMPS; the latter is required for p53 stabilization in response to genotoxic stress or upon nucleotide depletion. Nuclear translocation of GMPS in these conditions facilitates p53 stabilization by promoting its transfer from MDM2 to a multiprotein complex containing GMPS and the USP7 (also called HAUSP) deubiquitylating enzyme [105]. In addition, p53 inhibits DNA synthesis in a p21-independent, but SP1-dependent manner, by repressing the transcription of *deoxyuridine triphosphate nucleotidohydrolase* (*dUTPase*), which gene product catalyzes the hydrolysis of dUTP into dUMP, a precursor of dTTP [106]. On the other hand, p53 activates ribonucleotide reductase (RNR) upon DNA damage, an enzyme reducing nucleotide diphosphates (NDPs, including ADP, GDP, CDP, and UDP) at

the 2′ position of the ribose sugar to generate deoxyribonucleotides (dNTPs). RNR is a tightly regulated tetrameric enzyme consisting of two catalytic subunits (RRM1) and two regulatory subunits, either RRM2 or p53R2/RRM2B, that supplies cells with dNTPs for DNA replication or for DNA repair and mitochondrial DNA synthesis. p53 activates the transcription of *p53R2/RRM2B*, thereby contributing to its role in DNA repair [107,108]. Paradoxically, p53 was reported to suppress RRM1 and RRM2 expression at the post-transcriptional level via the inhibition of mammalian target of rapamycin complex 1 (mTORC1) [109]. It is notework that opposing roles of p53 in nucleotide synthesis have been described during amino-acid deprivation. Indeed, whereas p53 inhibits nucleotide synthesis when an exogenous source of serine becomes limiting, it sustains nucleotide synthesis during glutamine deprivation [89,90]. Finally, p53 can also modulate nucleotide synthesis indirectly through the regulation of the PPP and the one carbon cycle [15]. Hence, although several lines of evidence suggest that p53 coordinates the DNA repair machinery with nucleotide synthesis, further studies are needed to provide definitive conclusions about its exact functions in nucleotide metabolism.

2.7. p53 and REDOX balance

The control of ROS levels is certainly not the only mechanism by which p53 limits carcinogenesis but its importance is supported by *in vivo* data showing that tumor incidence in *Trp53* KO mice is significantly attenuated when these animals are supplemented with the ROS-scavenger N-acetyl-cysteine (NAC) [110]. In agreement with these findings, the Super-p53/ARF mice that have extra-copies of the *Trp53* and *Cdkn2a* tumor suppressor loci display a continuous activation of p53-dependent anti-oxidant genes that correlates with extended lifespan and reduced cancer incidence [111]. Under physiological conditions, different metabolic functions of p53 can limit ROS levels, including those that promote mitochondrial integrity, or through the down-regulation of ROS-generating enzymes such as nitric oxide synthase 2 (NOS2) [112]. In addition, p53 prevents ROS accumulation by controlling the transcription of genes encoding several important ROS-detoxifying enzymes. These p53-target genes include *Superoxide Dismutase 2* (*SOD2* or *Mn-SOD*), the gene product of which prevents the accumulation of superoxide radicals (O_2^-) in the mitochondria by converting them into H_2O_2 [113]. In retinal ganglion cells, p53 stimulates the transcription of *Catalase*, and it was also reported to regulate catalase activity via a direct protein—protein interaction and by controlling the expression of p53R2/RRM2 [114,115]. By regulating catalase activity, p53 promotes the degradation of H_2O_2 into water and free oxygen. In addition, p53 is intrinsically linked to glutathione metabolism through the transcriptional regulation of *Glutathione Peroxidase 1* (*GPX1*) and genes involved in several metabolic pathways that contribute to glutathione biosynthesis such as *SLC7A11* and *GLS2*, as well as by channeling serine/glycine towards GSH production at the expense of nucleotide synthesis [20,21,79,89]. p53-target genes that favor NADPH production through the PPP, such as *TIGAR* and *PFKFB3*, participate in the maintenance of a reduced GSH pool [12,46]. *SESN1* and *SESN2* belong to p53's anti-oxidant arsenal through their direct effect on peroxiredoxin proteins, by stimulating the degradation of KEAP1, an inhibitor of NRF2, and through the regulation of the AMPK-mTOR pathway [116—119]. Finally, other p53 direct target genes such as the uric acid transporter *SLC2A9/GLUT9*, *TP53INP1*, and *ALDH4* also contribute to p53 anti-oxidant activities through different mechanisms [95,120—123].

Nevertheless, there is also clear evidence that p53 can paradoxically increase ROS production. A plausible explanation regarding the divergent roles of p53 in controlling ROS levels is that p53 prevents

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oxidative damages and promotes their repair in order to favor cell survival in response to moderate ROS levels, but increases the production of ROS to lethal levels to induce several forms of cell death, including ferroptosis, apoptosis, and necrosis. The pro-oxidant effects of p53 that lead to cell death involve the transcriptional activation of genes encoding proteins with ROS-generating capacities including *LGALS7 (PIG1)*, the *NADPH-quinone oxidoreductase homolog TP53l3 (PIG3)*, and *neutrophil cytosol factor 2 (NCF2/p67phox)*, a gene encoding a component of NADPH oxidase, the critical enzyme responsible for cytosolic O_2^- production [96,124]. p53-mediated control of *PRODH/POX* also contributes to produce ROS by the ETC during p53-induced apoptosis [99]. Paradoxically, p53 has also been reported to repress *SOD2* promoter by binding to its transcriptional activator SP1 [125]. The complex interplay between p53 and SOD2 is also illustrated by p53's ability to translocate to mitochondria, where it binds and blocks the ROS-scavenging activity of SOD2 [126]. Stabilization of the pro-oxidant molecule p66^{shc} by p53 increases mitochondrial ROS levels and p53-dependent cell death [127]. The enhanced recruitment of p53 in mitochondria through its interaction with DRP1 has also been associated with mitochondria fragmentation, increased mitochondrial ROS levels, and decreased viability of neuronal cells in patients with huntington disease [128]. Finally, apoptosis can be initiated by p53 independently of its transcriptional activity through its binding to BCL2 family members at the outer mitochondrial membrane, leading to the subsequent release of cytochrome C from the ETC and to electron leak [129,130].

Strikingly, a strong body of evidence indicates that p53 transcriptional activity is modulated in response to oxidative stress, thereby defining an important feedback-loop. Several cysteine residues (including Cys 124, 141, 176, 238, 242, 277) located in the DNA binding domain of p53 are targets for redox regulation and p53 binding to its responsive elements is clearly dependent on reducing conditions. Moreover, the Apurinic/apyrimidinic endonuclease 1/reduction-oxidation factor 1 (APE1/Ref-1) protein has been shown to influence the DNA binding properties of several transcription factors, including p53, by maintaining specific cysteine residues in the reduced state [131–133]. p53 activation during oxidative stress involves its trafficking through nuclear structures that sense ROS called Promyelocytic Leukemia (PML) nuclear bodies. Increased sumoylation of p53 in PML bodies, as well as that of several of its regulators (ARF, MDM2, HIPK2, CBP), has been associated to the induction of p53-regulated anti-oxidant genes [134,135]. Interestingly, *PML* was also identified as a p53 direct target gene [136], highlighting a potential feedforward mechanism that contributes to p53-mediated senescence, a process during which ROS play a central role. Interestingly, oxidative stress can also promote the translocation of p53 to the mitochondrial matrix where it interacts with cyclophilin D, a key regulator of the mitochondrial permeability transition pore (mPTP), resulting in dissipation of the mitochondrial membrane potential ($\Delta\Psi$m) and triggering necrosis in neuronal cells during ischemia-reperfusion injury [137].

2.8. p53-mediated regulation of autophagy

There is a complex interplay between p53, autophagy, and cancer. Basal autophagy is an evolutionary conserved quality control process but this catabolic self-eating program can be induced to provide essential metabolites when other sources of nutrients become limiting. p53 functions in autophagy involves transcriptional and non transcriptional effects that have been mainly studied in the context of cancer cells although it is likely that they also contribute to normal tissue homeostasis. Several components of the autophagy machinery have been identified as direct p53 target genes including genes encoding proteins of the autophagy core machinery, autophagy regulators, and lysosomal proteins [39,138–141]. p53 was also found to control autophagy through the AMPK-mTOR pathway [142]. The transcriptional activation of autophagic genes by nuclear p53 has been linked to its ability to induce cell death during genotoxic stress, but, paradoxically, cytoplasmic p53 was shown to repress autophagy [143]. In agreement with the inhibitory role of p53 on autophagy, depletion of *Cep-1*, the nematode ortholog of p53, triggers autophagy and increases life span in *Caenorhabditis elegans* [144]. Altogether, these data suggest that both activation and inhibition of p53 can trigger autophagy. In addition, p53 is involved in a feedback loop in which the ATG7 protein modulates p53 functions, likely to restrain its pro-apoptotic activities and to maintain cellular homeostasis during mild metabolic challenges. In agreement with this notion, in absence of the ATG7 protein, nutrient-starved cells exhibit impaired cell-cycle arrest but are more prone to p53-induced cell death, a process that was linked to ATG7 direct binding to p53 and its co-recruitment to the *p21^{Cdkn1a}* promoter [145]. It is therefore plausible that p53 somehow senses decreased autophagic flux through several mechanisms and modulates its transcriptional program to compensate for such defect in order to facilitate cell survival. However, p53 can stimulate autophagy to ultimately kill cells, a mechanism aiming at preventing the survival of cells accumulating damages. The complex connections between p53 and autophagy in cancer development have been illustrated in several cancer-prone animal models. In a mouse model of hereditary breast cancer based on *Palb2* inactivation, loss of *Atg6/Beclin 1* reduced tumorigenesis and extended the lifespan of *Palb2*-deficient mice, an effect that was mitigated by the concomitant inactivation of *Tp53* [146]. In addition, *Atg7* or *Atg5* deficiency reduced tumor burden by turning on p53 in a KRAS^{G12D}-driven lung cancer model [147]. Finally, in a model of activated KRAS-driven pancreatic cancer, the dual role of autophagy in cancer progression was shown to be intrinsically connected to the p53 status. Thus, whereas inhibition of ATG7 favored the developement of pre-malignant intraepithelial neoplasias but blocked their evolution into pancreatic ductal adenocarcinoma (PDAC), it accelerated tumor onset in absence of p53 [148]. Based on these data, it is currently difficult to provide a unifying model of p53 functions in autophagy. A more detailed analysis of p53 functions in the different types of autophagy (macroautophagy versus selective forms of autophagy) is required to unvail its subtle roles in this key cellular process (See Table 1).

3. P53: A METABOLIC SENSOR INVOLVED IN MULTIPLE SIGNALING PATHWAYS

As described in other parts of this review, p53 activities are modulated in response to many metabolic challenges. Moreover, it plays a central role in metabolism by acting upstream and downstream of key signaling pathways that sense and control the energetic status of cells.

3.1. p53 and LKB1-AMPK-mTOR signaling

Given its pleiotropic roles in metabolism, it is not surprising that p53 plays an important role in the LKB1-AMPK-mTOR pathway, a central energy sensing pathway that coordinates cell metabolism. Multiple evidences indicate that p53 and the LKB1-AMPK-mTOR pathway are intimately intertwined, although the effect of p53 on this pathway depends on the stress situation. Thus, p53 was initially shown to be activated by AMPK during energetic stress through its phosphorylation on serine 15 [87,142,149]. However, depending on the cell type, the increased phosphorylation of p53 on Ser15 (Ser18 in the mouse) that occurs upon glucose deprivation was attributed either to AMPK or to

ATM, another kinase activated in response to oxidative stress and DNA damage [23,87,150]. It is interesting to note that knock-in mice expressing a mutant form of p53 that cannot be phosphorylated on Ser 18 (S18A) exhibit metabolic phenotypes and defects in glucose homeostasis, providing further evidence for the involvement of p53 phosphorylation on this key residue in metabolism [151]. At the other end of this metabolic feedback loop, it is well known that p53 modulates LKB1-AMPK-mTOR signaling during genotoxic stress or glucose deprivation through the transcriptional control of *Liver Kinase B1* (*LKB1/STK11*), *AMP-kinase β1* (*AMPKβ1*), *DNA Damage inducible transcript 4 (DDIT4/REDD1)*, *SESN1/2*, and *TSC complex subunit 2* (*TSC2*), thereby leading to inhibition of mTORC1 and decreased cell growth [118,152–156]. Paradoxically, p53-proficient cancer cells respond to glutamine deprivation by inducing a rapid adaptive response that sustains arginine levels and mTORC1 activity, indicating that the crosstalks between p53 and mTORC1 are complex and stimulus-specific [91].

3.2. p53 and the insulin-PI3K-AKT pathway

There is a well-described reciprocal interplay between AKT and p53. p53 induction leads to potent inhibition of AKT signaling by activating the transcription of *Phosphatase and Tensin Homolog* (*PTEN*), a gene encoding a PIP3 phosphatase that opposes the effects of PI3K, *IGF-binding protein 3* (*IGFBP3*) that produces a secreted protein binding to free IGF1, and *Phlda3*, the gene product of which blocks AKT translocation to the plasma membrane [152,157–159]. The impact of p53 on this signaling cascade also involves the transcriptional repression of the *Insulin Receptor* and *Insulin-like Growth Factor Receptor 1* [160]. In addition, p53-mediated regulation of the abundance of mono-unsaturated phospholipids through the repression of *SCD1* also influences indirectly AKT activity [50]. The links between AKT and the p53 pathway are also illustrated by AKT-mediated phosphorylation of MDM2, the key negative regulator of p53 [161,162]. Interestingly, p53-mediated regulation of *PTEN* (and *TSC2*) occurs preferentially in tissues that respond to exogenous glucose levels, including heart, muscle, liver, white adipose tissue (WAT), and kidneys, suggesting that the regulation of the AKT and mTOR signaling cascades by p53 is an important component of its nutritional sensing functions *in vivo* [152].

3.3. p53 and hypoxia

Under low oxygen conditions, cells rapidly adapt their metabolism by stabilizing the HIF-1α transcription factor, but it is now recognized that p53 also contributes to the adaptive response of cells to hypoxia. Modulation of p53 activities during hypoxia occurs through both HIF-dependent and independent mechanisms. Several groups have linked HIF induction to decreased MDM2-mediated ubiquitination of p53, an effect that controls its nuclear export and proteasome-mediated degradation [163–166]. Other HIF-dependent mechanisms have been proposed, such as the control of p53 translation by the HIF-inducible RNA-binding protein HuR [167]. However, other investigators have shown that ATR can phosphorylate and activate p53 during S phase independently of HIF1α in low oxygen conditions [168]. Other mechanisms linked to hypoxia, such as the production of mitochondrial ROS or the associated acidosis, can also stabilize p53 [169,170]. Coordination of HIF and p53 activities during hypoxia involves a complex network of common regulators in which the Von Hippel Lindau (VHL) tumor suppressor and the MDM2 oncoprotein play a central role. The complex relationship between HIF, VHL, MDM2, and p53 allows cells to adapt their response to different oxygen

concentrations. As for many adaptive responses in which p53 is involved, the fine tuning of this network is important to either promote its pro-survival effects in transient hypoxic conditions or trigger cell death upon more severe or prolonged hypoxia. From a metabolic standpoint, HIF and p53 display opposite effects on glycolysis and mitochondrial respiration and it is therefore logical that the activities of these two transcription factors are coordinated during hypoxia. Thus, whereas HIF stimulates glycolysis by inducing the expression of most glycolytic enzymes and glucose and lactate transporters, p53 represses glycolysis by various mechanisms described in section 2.1. These two transcription factors also mediate antagonistic activities on mitochondrial respiration. Some of their effects on this OXPHOS to glycolytic switch involve the transcriptional regulation of pyruvate dehydrogenase kinases (PDKs) that inhibit mitochondrial pyruvate oxidation as well as the assembly/activity of the ETC [171–174]. Intuitively, induction of p53 during hypoxia should balance some of the metabolic effects mediated by HIF1α. However, the p53 response to mild hypoxic conditions seems to be initially biased towards a subset of its repressed target genes, a process implicating the mSin3a co-repressor [175]. Competition between HIF1α and p53 for common transcriptional co-activators such as CBP/p300 and specific post-translational modifications of p53 also seem to play a role in p53's ability to regulate a subset of its target genes during hypoxia [176,177]. Nevertheless, during more severe and/or prolonged hypoxia that can lead to the accumulation of DNA damage, p53 turns on a cell death program that is mediated, at least in part, by *Bnip3L* and *NIX* [178,179]. It is noteworthy that HIF and p53 are key regulators of intracellular ROS levels, but their activities are also responsive to redox changes, thereby defining an additional feedback loop that contributes to the cellular response to hypoxia.

3.4. Connections between p53, AcCoA and NAD metabolism

There is an important crosstalk between p53, NAD, and AcCoA metabolism. Indeed, an important aspect of p53 functions relates to its acetylation on key residues involved in different important domains of the protein, including its DNA binding domain and the c-terminal regulatory domain. The acetylation status of p53 reflects the activity of different enzymes that acetylate or deacetylate p53 on specific residues. Several acetyltrasferases (P300, CBP, hMOF, TIP60) and deacetylases (HDAC1/8, SIRT1), define a complex regulatory network standing at the interface between metabolism and p53 since their co-factors, AcCoA for acetyltransferases and NAD for sirtuins, are also key metabolites [180–183]. Interestingly, pyruvate oxidation by the PDH and FAO, two important metabolic pathways targeted by p53, regulate AcCoA abundance. Although this has not been proven yet, the control of AcCoA levels by p53 likely contributes to maintain cellular homeostais since many metabolic enzymes are regulated by acetylation [184,185]. NAD metabolism also plays a pivotal role in the p53 network. NAD^+ binds to p53 tetramers with a millimolar range affinity constant, inducing a conformational change and modulating p53 DNA binding specificity [186]. Similarly to the AcCoA-p53 interplay, several metabolic pathways regulated by p53 can modulate the NAD^+/NADH ratio, and changes in NAD levels directly impact on the activity of SIRT1, a NAD-dependent class III deacetylase that is highly connected to p53 [187]. SIRT1 acts as a signalling hub, linking stress/nutrient sensing pathways such as the p38, mTOR, and AMPK pathways to p53. SIRT1-mediated deacetylation of p53 represses its transactivation activity in both normal and cancer cells. Consistent with this notion, SIRT1 deficiency leads to p53 hyperacetylation and enhances the DNA-damage response in lymphocytes [188]. SIRT1-mediated control of p53 acetylation was also shown to regulate its subcellular localization and its transcription-independent mitochondrial

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functions [189]. Of note, SIRT1 substrates include acetyltransferases that target p53, including p300 and TIP60, as well as several metabolic enzymes controlling AcCoA availability, such as ATP-citrate lyase (ACLY) and AcCoA synthetase 1 (ACSS1) [190]. Finally, additional levels of regulation of this network involve p53-mediated repression of *SIRT1* promoter, and the regulation of several miRNAs by p53 that bind to the 3′-UTR of *Sirt1, Sirt2, Sirt6,* and *Sirt7* mRNAs and inhibit their translation [191—194].

3.5.   p53 and PGC1α

Several studies have highlighted important links between p53 and the transcriptional co-activator Peroxisome proliferator-activated receptor Gamma, Coactivator 1 alpha (PGC1α), an important metabolic regulator. Depinho and colleagues showed that p53 inhibits the transcription of *PGC1α* (and *PGC1β*) in cells undergoing premature aging in the setting of telomere dysfunction [195]. Moreover, a direct interaction between PGC1α and p53 that promotes p53's transcriptional activities and influences cell fate in response to metabolic challenges was also reported. Thus, in glucose-deprived hepatocytes, PGC1α favors the induction of p53 target genes involved in cell cycle arrest and metabolism at the expense of pro-apoptotic genes, likely to initially protect cells and allow them to adapt to nutrient starvation. When PGC1α was inhibited in this experimental model, p53 then induced a cell death response [196]. Conversely, p53 binding to PGC1α in adipocytes was also shown to repress PGC1α activity on its target genes, including *Ucp1*, a gene encoding a proton channel that uncouples the electron transport chain with ATP production to favor heat production in brown adipocytes [197]. It is interesting to note that in metabolically challenged cells, p53 also activates the transcription of *LPIN1*, a gene encoding a bifunctional protein that acts as a nuclear transcriptional co-activator with PGC1α and Peroxisome proliferator-activated receptors (PPARs) to promote FAO or behave as a phosphatidate phosphatase enzyme that catalyzes the conversion of phosphatidate to diacylglycerol, a key step in the biosynthesis of triacylglycerol [23]. Hence, p53, PGC1α and their co-factors define a finely tuned network that allows cells to mount transient adaptive responses upon metabolic challenges, before engaging cells into a more detrimental fate when these stresses increase in intensity.

4.   CONTRIBUTION OF P53-ASSOCIATED METABOLIC FUNCTIONS TO NORMAL TISSUE HOMEOSTASIS

We still lack an integrated vision of p53-associated metabolic functions at the whole organismal level but growing evidence suggests that the deregulation of p53 metabolic activities impacts normal tissue homeostasis, in particular under conditions of nutritional challenge. In line with p53 functions in multiple metabolic pathways, its deregulation results in dysfunction of major metabolic tissues such as skeletal muscles, liver, pancreas, and adipose tissue (See Figure 2).

4.1.   Role of P53-Associated metabolic functions in muscles

It is well-recognized that *Trp53* KO mice have an altered endurance capacity that reflects, at least in part, the importance of p53 in the control of oxidative phosphorylation and proper mitochondrial function in skeletal muscles [26,27,198]. p53 translocates to mitochondria during an acute bout of exercice where it binds to TFAM, a key regulator of mtDNA replication and transcription [27,199]. Both acute and chronic exercice have been shown to diminish *p53* mRNA levels,

Figure 2: Overview of the known *in vivo* metabolic functions of WT-p53 and the consequences of their deregulation on human diseases (beyond cancer). FA, Fatty acids; FAO, Fatty Acid Oxidation; PPP, Pentose Phosphate Pathway; ROS, Reactive Oxygen Species; ATP, Adenosine Tri Phosphate.

but concommitantly increase its phosphorylation [199]. Beside its role in respiration, mitochondrial p53 maintains the integrity of mitochondria in muscle cells by regulating mtDNA repair [200]. Several metabolic activities of p53, among which are its aforementioned anti-oxidant functions that protect muscle cells from respiration-linked ROS production, and its role in mitochondrial biogenesis, ensure proper myocyte function on the long term [201]. These data suggest that maximal aerobic capacity and mtDNA integrity in muscle cells involve distinct pools of the p53 protein that control the transcription of genes encoded either by the nuclear or the mitochondrial genomes. The role of the p53 pathway in cardiac cells has been poorly investigated but the finding that p53 controls the expression of genes related to mitochondrial activity and biogenesis, oxidative phosphorylation and FAO, cardiac architecture, and excitation-contraction coupling in adult cardiomyocytes raises important questions regarding its physiological role in heart and potential implication in cardiovascular diseases. Consistent with this notion, *p53* inactivation in adult murine cardiomyocytes results in cardiac hypertrophy and increased expression of markers of heart failure [202]. Nevertheless, p53 can shift from a death promoting function in cardiomyocytes to a pro-survival activity upon reoxygenation in a model of infarcted heart, an effect that was linked to its acetylation on K118 by TIP60 and differential binding to *Bax* and *Nos3* promoters [203].

4.2. Role of P53-Associated metabolic functions in liver

Another tissue in which p53-metabolic functions play an important physiological role is the liver [204]. p53 is strongly induced in hepatocytes during fasting in an AMPK-dependent manner, but p53 is also activated in liver in conditions of nutrient excess [205—207]. p53 has been linked to several key metabolic pathways in hepatocytes, but conflicting results preclude a definitive conclusion about its exact functions in liver. In contrast to its positive role on mitochondrial respiration in most cell types, a peculiarity of liver-p53 is to inhibit pyruvate transport in the mitochondria and to decrease OXPHOS, a process implicating the binding of its well-described target, PUMA, with the pyruvate transporter MPC2 [208]. Other data support both positive and negative effects of p53 on gluconeogenesis. On one hand, p53 was proposed to control the expression of SIRT6, interfering with the nuclear localization and transcriptional activity of FOXO1, a key regulator of a gluconeogenic program that includes *phosphoenolpyruvate carboxykinase 1* (*PCK1*) and *Glucose-6-phosphatase* (*G6PC*). Accordingly, these investigators showed that *Trp53* KO animals display an improved response to the pyruvate tolerance test that is commonly used to measure the gluconeogenic ability of hepatocytes. Moreover, fasted mice expressing ectopic p53 in liver exhibit impaired gluconeogenesis after injection of a bolus of pyruvate [209]. On the other hand, several groups have shown that gluconeogenesis is altered in *Trp53* KO mice under conditions of nutrient starvation [196,210]. In agreement with the role of p53 in promoting gluconeogenesis, the Rotter laboratory reported that pharmacological stabilization of p53 by Nutlin3A in human hepatocarcinoma HepG2 cells induces a gluconeogenic program that includes *PCK2, G6PC, Glycerol kinase* (*GK*)*, Aquaporins 3 and 9*. The same authors also showed that primary hepatocytes isolated from p53-deficient mice exhibit impaired gluconeogenesis *ex vivo* [211]. In addition, acute inactivation of *Tp53* in hepatocytes of adult mice has been shown to decrease glycogen storage and to impair gluconeogenesis, although the latter phenotype was attributed to altered amino-acid catabolism, an important gluconeogenic process, rather than to decreased *PCK/G6PC* expression [205].

Other investigators have linked changes in p53 activity in hepatocytes to other aspects of glucose metabolism. Thus, knock-in mice expressing the p53 S18A mutant exhibit glucose intolerance and insulin resistance in a hyperinsulinemic-euglycemic clamp test. These phenotypes, that were only observed in 6-month-old mice but not in younger animals, were rescued upon administration of an anti-oxidant, suggesting that this defect is an indirect consequence of chronic oxidative stress in these animals [151]. Consistent with this notion, mice with increased gene dosage of *Trp53* display improved glucose tolerance, an effect that is possibly associated to the enhanced expression of anti-oxidant genes regulated by p53 in this animal model [111,212].

One common phenotype found in animal models with perturbed p53 activity is hepatosteatosis, a process that results from abnormal accumulation of triglycerides in hepatocytes. Paradoxically, both p53 activation and inactivation result in liver steatosis through different mechanisms, and nutrient state influences this phenotype. Thus, animals harboring a germline deletion of *Trp53* display liver steatosis when fed a high fat diet (HFD) [213]. This phenotype is due, at least in part, to the impaired regulation of the p53-target gene *Aromatase* which encodes a key enzyme involved in the conversion of testosterone into 17β-estradiol, leading to an increase in testosterone over estradiol levels and triglyceride accumulation [213]. Although expression of ectopic aromatase was shown to rescue hepatosteatosis of *Trp53* KO males under HFD, it is likely that other metabolic activities of p53, such as p53-mediated repression of fatty acid synthesis, also contributed to this phenotype. Using *Trp53* conditional KO mice, it was also shown that acute inactivation of p53 in adult hepatocytes rapidly induces liver steatosis in fed animals, indicating that this phenotype is not a long-term consequence of p53 loss [205]. Paradoxically, pharmacological inhibition of p53 by pifithrin α p-nitro (PFTα) limits HFD-induced hepatosteatosis by promoting FAO. This metabolic effect was associated to the down-regulation of the p53-responsive miR34a that targets *SIRT1* mRNA. PFTα-induced stabilization of SIRT1 in turn facilitates *Malonyl-Coenzyme A Decarboxylase* (*MCD*) transcription by activating PGC1α-PPARα and inhibits AcetylCoA Carboxylase (ACC) activity through the LKB1-AMPK cascade, thereby leading to decreased amount of Malonyl-CoA and, consequently, to the activation of CPT1, a mitochondrial fatty acid transporter that fuels FAO [214]. Interestingly, p53 function in lipid metabolism also plays an important role in hepatocytes in conditions where nutrients are limiting. Indeed, hepatocytes respond to nutrient starvation by limiting ribosome assembly and function, one of the most energy consuming biological processes in cells, in part through the activation of the Impaired Ribosome Biogenesis Checkpoint (IRBC). During this physiological response to nutrient deprivation, non-assembled ribosomal proteins bind to MDM2 and inhibit its interaction with p53, thereby unleashing p53 activity. Using an elegant mouse model in which MDM2 function in the ribosomal stress response was compromised, p53 was shown to promote FAO during nutrient starvation by stimulating *MCD* transcription [22]. A recent observation has linked WT-p53 to the regulation of the mevalonate pathway in hepatocytes through the transcription of *ABCA1*, a gene encoding a retrograde cholesterol transporter that influences SREBP2 maturation and its nuclear translocation [45]. p53 can also influence reverse cholesterol transport through the transcriptional control of *Caveolin1* (CAV1), which gene product directly interacts with ABCA1 [215]. This p53-ABCA1-SREBP2 cascade was initially identified in the context of hepatocellular carcinoma (HCC) initiation [45]. However, given the important ramifications of this key metabolic pathway in cholesterol metabolism, and in steroid hormones, non-sterol isoprenoids, and Coenzyme Q synthesis, it is likely

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to be implicated in some of the metabolic changes associated with perturbed p53 activity *in vivo*. Finally, as already mentioned, p53 modulates ureagenesis through repression of *CPS1*, *OTC* and *ARG1*, three key enzymes of the urea cycle, a major detoxifying process that takes place in liver. In agreement with these findings, p53-deficient animals display increased urea levels in liver, serum and urine upon administration of NH4Cl [102].

More work is needed to further understand the importance of p53 in the regulation of each of these key liver functions and evaluate their role in human pathologies beyond cancer. Nevertheless, these data indicate that the contribution of p53 to proper liver homeostasis involves multiple metabolic pathways and is highly dependent on the nutritional status.

4.3. Role of P53-associated metabolic functions in adipose tissue
Converging evidence supports the notion that p53 is an important regulator of adipose tissue (AT) function. The roles of p53 in AT are multiple, including the control of whole body energy metabolism, thermo-regulation, inflammation, senescence, protection against lipotoxicity, and the regulation of insulin sensitivity. Some of these activities have been extensively documented in previous reviews, so we focus in this section on the role of p53 in adipocyte differentiation and on its metabolic activities, which represent an important facet of p53 functions in AT [216,217]. Several reports suggest that p53 plays different roles in white versus beige/brown adipocytes, which are distinct populations of adipocytes with specialized activities in fatty acid storage or lipid catabolism and heat generation, respectively. Independent laboratories have shown that p53 restricts differentiation into the white adipocyte lineage through several mechanisms including the regulation of C/EBPα and PPARγ, two major regulators of adipocyte differentiation. In line with this notion, p53-deficient Mouse Embryonic Fibroblasts (MEFs) and pre-adipocytes differentiate more efficiently into mature adipocytes *in vitro,* whereas expression of ectopic p53 impairs adipocyte differentiation [197,218—220]. However, p53 functions in mature adipocytes extend beyond the regulation of differentiation. Indeed, p53-associated metabolic activities, including the control of NADPH production by malic enzymes or by the PPP, and the inhibition of SREBP-mediated regulation of genes involved in de novo fatty acid synthesis, likely synergize to limit lipid anabolism in adipocytes [42,221]. Despite these consistent findings based on *in vitro* experiments, the *in vivo* function of p53 in adipocytes remains confusing. Indeed, phenotypic analysis of *Trp53* KO animals have led to very distinct conclusions, in particular when these animals were challenged on a HFD. Thus, although two groups reported an increased tendency of *Trp53* whole-body KO animals to accumulate more fat mass when fed a HFD [213,222], others teams showed that these mice gain less weight under HFD [197,223]. In the latter studies, the resistance of *Trp53* KO mice to HFD-induced obesity was linked to increased energy expenditure, an effect correlated with enhanced expression of the uncoupling protein 1 (UCP1) that promotes the thermogenic potential of brown and beige adipocytes [197,223]. Although these results appear contradictory, it is plausible that housing conditions of these animals (at room temperature versus at thermoneutrality) dramatically influenced the outcome of p53 deficiency. In contrast to the above described data suggesting an inhibitory role of p53 on brown/beige adipocytes, several lines of evidence support the notion that p53 enhances their activity. Thus, p53 was proposed to promote brown adipocyte differentiation and function during embryonic development, in part through the direct transcriptional induction of key BAT regulators, including *Prdm16* and *Elovl3*. Thus, Rotter and colleagues showed that *Trp53* KO E18.5 embryos display altered

expression of BAT markers, including PRDM16 and UCP1, and brown adipocyte differentiation *in vitro* was impaired upon p53 knock-down [222]. The role of p53 in promoting brown adipocyte function and the browning of white adipocytes is also supported by the analysis of a GEMM in which inactivation of *Mdm4* was used to activate a p53-acetylation mutant (p53^{3KR}) that is defective for the induction of its senescence, cell death and cell cycle programs, but still proficient for the regulation of some of its metabolic target genes. These compound animals exhibit increased energy expenditure and a marked protection against HFD-induced obesity, a phenotype associated with the ability of p53^{3KR} to promote the expression of brown adipocyte markers, including *Elovl3*, an elongase involved in the elongation of long-chain fatty acids, and genes involved in FAO and mitochondrial respiration uncoupling (*Cpt-1b*, *Ucp1*, *Pgc1α*) [224]. Furthermore, viral delivery of WT-p53 in adult brown adipocytes increases the thermogenic capacity of mice and limits weight gain under HFD. Conversely, inhibition of p53 transcriptional activity leads to decreased expression of several thermogenic markers, including UCP1, and results in increased body weight [223]. In conclusion, although these data point to an important role for p53 in adipocytes, further work is needed to fully delineate the complex activities of p53 in adipocytes and the control of whole body energy homeostasis.

4.4. p53 functions in pancreas
p53 tumor suppressor functions in pancreatic cancer have been extensively studied in pancreatic cancer, but much less is known about the metabolic functions of p53 in the endocrine pancreas. p53 activity is induced in pancreatic β-cells in diabetic patients as well as in rodent animal models of type II diabetes, and p53 was shown to be important for β-cell proliferation and survival [225—229]. In contrast to its recognized role in promoting OXPHOS in many cell types, p53 inhibits mitochondrial respiration and calcium signalling in pancreatic β-cells, thereby limiting glucose-stimulated insulin secretion and leading to glucose intolerance. This effect was linked to its ability to repress the expression of *pyruvate carboxylase* (*PC*) that resulted in reduced oxaloacetate (OAA) levels [230].

5. P53 FUNCTIONS IN OBESITY, TYPE II DIABETES AND NAFLD

Many of the aforementioned studies support the idea that perturbations of p53-associated metabolic functions play a significant role in obesity, as well as in two of its common consequences, type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD). Consistent with its role in obesity, p53 protein levels increase in rodent models of obesity as well as in human obese individuals [207,221,231,232]. The notion that p53 is implicated in metabolic disorders independently of its tumor suppressive functions is supported by epidemiological studies showing that the single nucleotide polymorphism (SNP) located at position 72 of the human *TP53* gene associates with increased risk of T2D, but not with cancer predisposition [233,234]. The metabolic dysfunctions associated with this SNP were confirmed in a humanized mouse model that was used to study the differential effects of the P72 versus the R72 alleles. These authors showed that knock-in mice expressing the p53 R72 allele exhibit impaired regulation of a subset of p53 target genes (including *Tnf*, *Pck1*, *Ccl2* and *Npc1l1*), and were more susceptible than mice expressing the P72 allele to obesity and glucose intolerance when fed a HFD [235].

Although there is currently no clear clinical evidence that p53 directly contributes to type I diabetes, perturbations of p53-associated functions in experimental models can lead to several key biological processes that underlie diabetes, including loss of pancreatic β-cells,

pertubations of glucose homeostasis at the organismal level, and insulin resistance in peripheral tissues. Several groups have reported that p53 activation in response to various insults, including oxidative stress and increased free-fatty-acids levels, leads to cell death of pancreatic β-cells [225–229,236]. Moreover, by directly regulating glucose uptake, glycolysis, and gluconeogenesis, p53 impacts glucose metabolism in peripheral tissues. p53-mediated alteration of glucose homeostasis can lead to increased levels of circulating glucose, a hallmark of T2D. Finally, as already mentioned, p53 activity and the insulin-PI3K-AKT signalling pathway are intertwined in various cell types, in particular in peripheral tissues that respond to insulin to regulate glucose metabolism such as skeletal muscles, heart, WAT, liver and kidneys [152]. Other aspects of p53 functions influence insulin sensitivity in a cell-autonomous manner as well as through autocrine loops. Thus, the pro-inflammatory activities of p53 in AT that are stimulated by nutrient excess impair insulin sensitivity [231,237]. However, the relationship between p53, the immune system and diabetes is complex since administration of Nutlin3A, which results in p53 activation, was shown to ameliorate the severity of streptozotocin-induced diabetes through a mechanism implicating IL12p40 secretion and the regulation of the immune system [238]. Interestingly, the stabilization of p53 in AT under HFD can reprogram distantly liver gluconeogenesis, thereby amplifying glucose homeostasis defects that ultimately lead to insulino resistance [231]. Another interesting aspect by which p53 influences glucose homeostasis involves the crosstalk between angiogenic cells and skeletal muscles. Indeed, endothelial cell-specific inactivation of *Trp53* limits the impaired production of nitric oxide (NO) that occurs under HFD, leading to improved glucose consumption in surrounding muscle cells, a process that was linked to increased expression of PGC1α and mitochondrial biogenesis in these cells. Conversely, p53 activation resulting from *Mdm4* inactivation in endothelial cells impaired insulin sensitivity and glucose tolerance [239]. Finally, p53-mediated control of the orixegenic hormone ghrelin in the central nervous system can influence feeding behaviors, thereby contributing to obesity and its related metabolic disorders [240].

NAFLD is a common manifestation of obesity and metabolic syndrome. NAFLD includes a large spectrum of pathological changes, ranging from benign hepatosteatosis (fatty liver) to its more severe manifestation, non-alcoholic steatohepatitis (NASH), a recognized risk factor for hepatocellular carcinomas (HCCs). Many stresses associated with chronic liver injury such as metabolic disturbances, iron deposition, or high saturated fatty acid concentration can induce p53 activity. Conversely, many perturbations of p53 activities can also contribute to each of these liver defects. Consistent with its role in liver disease, p53 protein levels in hepatocytes correlate with the severity of steatosis in NAFLD patients and p53 induction has been reported in several mouse models of NAFLD [206,241–243]. One of the key questions in this field relates to the potential clinical interest of therapeutic strategies aiming at modulating p53 activities for NAFLD and diabetes. As already described, different studies based on genetic inactivation of *Trp53* in mice fed a HFD led to very different conclusions regarding the accumulation of fat mass. Nevertheless, p53 deficiency improves various symptoms associated with liver injury in animal models of NAFLD, including fibrosis [206,242,244]. Although these data have interesting clinical perspectives, long-term inhibition of p53 in patients is not an option given its potential dramatic side effects on tumor predisposition. Nevertheless, pharmacological inhibition of p53 using PFTα, even for a short period of time, has been shown to improve liver steatosis and insulin sensitivity in rodent models fed a HFD [207,214]. Paradoxically, moderate activation of p53 in hepatocytes obtained by administration of low doses of the DNA damaging agent doxorubicin improved diet-induced non-alcoholic steatosis and steatohepatitis in mice [245]. In addition, administration of Nutlin improves insulin sensitivity in an experimental model of T2D [238].

Altogether, these studies provide clear experimental evidence that p53 plays an important role in NAFLD and diabetes. However, they do not come with a definitive conclusion regarding which strategy (p53 activation or p53 inactivation) would provide the best clinical benefit to NAFLD and diabetic patients. Translating such strategies to the clinic will require a much deeper understanding of the mechanisms that fine tune p53 activities *in vivo* in order to design efficient, but also safe, therapies.
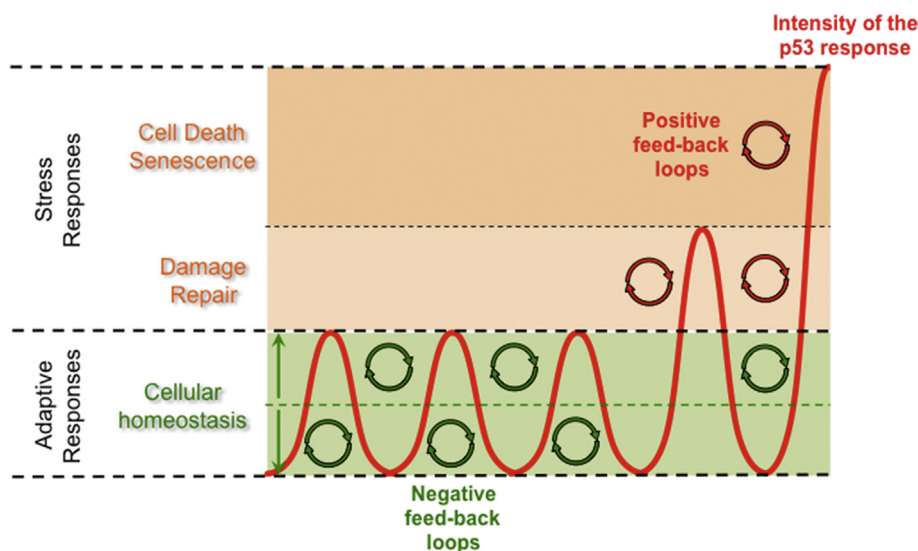

Figure 3: Role of the p53 network in adaptive and stress responses. The molecular mechanisms underlying p53's implication in adaptive versus stress responses are poorly understood. In the proposed model, multiple negative feed-back loops contribute to maintain the p53 response within a range of activity that favors cell survival and ensure proper cell homeostasis. When these stresses increase in intensity and/or duration, p53 gets recruited to a subset of its target genes that leads to the elimination of damaged cells.

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6. CONCLUSIONS

An impressive amount of data collected in the past twenty years have shed light on the importance of both WT-p53 and mutated forms of p53 in metabolism and showed that perturbations of these metabolic networks influence cancer progression but also contribute to various metabolic disorders. However, these studies have also underscored the complexity of p53-associated metabolic functions, leading sometimes to contradictory results that preclude definitive conclusions. Many parameters could explain these discrepancies, and it is noteworthy that a significant number of these studies have been performed using different cancer cell lines that have undergone multiple metabolic adaptations during the process of transformation, many of which impinge on p53-associated metabolic activities. In addition, as illustrated extensively in this review, p53 is a key sensor of metabolic changes and therefore, a particular attention should be payed to *in vitro* cell culture conditions when performing metabolism-related experiments because they can dramatically influence p53 activities. More suprisingly, conflicting results have also been reported when the metabolic functions of p53 were assessed *in vivo*, even sometime using the same animal models. One intriguing illustration of such opposite conclusions relates to the role of p53 in animals fed a HFD, a situation during which *Trp53* inactivation was shown to either promote or limit weight gain [197,213,222,223]. The *in vivo* function of p53 in gluconeogenesis is also a matter of debate [196,205,209—211]. More work is needed to understand these contrasting results, but it is plausible that different housing conditions of these animals (temperature, inverted light cycle, etc), specific genetic backgrounds, or distinct microbiota, influenced the control of key metabolic activities by p53. In light of these studies, it is becoming obvious that p53 functions in metabolism display some degree of cell-type specificity that is poorly understood but which is likely influenced by a number of factors, including the tissue-specific expression pattern of p53 regulators, as well as that of other p53 family members (p63, p73) that display important metabolic activities [246—248]. Moreover, the differential role of p53 isoforms in metabolism remains an unsolved question that requires more investigations. Finally, although in this review we mainly focused on the metabolic activities of WT-p53, the roles of p53 mutants in metabolism are also gaining momentum but require further investigation. Another aspect of p53 function in metabolism that requires clarification is the mechanism by which p53, and other components of the p53 pathway, coordinate their metabolic activities in different tissues to maintain energy homeostasis at the organismal level. Whether this level of coordination involves specific neurological signals, circulating metabolites, or secreted proteins regulated by p53 remains to be determined, but there is little doubt that the p53 pathway is playing an important role in coordinating whole body metabolism. Hence, in addition to its well-documented function in cancer and its recognition as the "guardian of the genome", it may be time to consider p53 as a "guardian of energy homeostasis."

Despite the large amount of work already performed in this field we still lack an integrated vision of p53-associated metabolic activities at the cellular level. Nevertheless, some general traits are emerging from past studies. First, in most cell types, p53 appears to limit glycolytic flux and coordinate it with branched anabolic pathways such as the PPP and the serine synthesis pathway, in part to maintain a proper redox state. p53 negatively regulates several anabolic pathways, including de novo fatty-acid synthesis, and concomitantly stimulates lipid catabolism (FAO). It is noteworthy that p53 is highly connected to lipid metabolism both at the systemic and cellular levels through multiple activities controlling lipid transport, storage, modification, and

utilization [43]. As a general mechanism to limit proliferation, it is possible that the overall function of p53 in amino-acid metabolism is to divert these building blocks away from protein synthesis. Another important function by which p53 influences metabolism as well as cell fate is through the control of iron metabolism [75]. p53 functions in these multiple metabolic pathways involve transcriptional as well as post-transcriptional mechanisms implicating different pools of the p53 protein exhibiting distinct subcellular localizations. The direct control of metabolic enzymes by p53 through protein—protein interactions raises puzzling questions given the relative stochiometry of these different proteins. A strong body of evidence also suggests that p53 promotes mitochondrial respiration in many cell types, with the exception of pancreatic β cells and hepatocytes [205,208,230] (Figure 3).

It is interesting to think about the links between p53 and metabolism from an evolutionary standpoint. The importance of p53 in nutrient storage and utilization is particularly intriguing in light of the natural selection processes that led to the emergence of gene networks that guarantee proper energy homeostasis during periods when food was limiting. The gene networks regulated by p53 play a pivotal role in adaptive responses to nutrient deprivation by promoting cell survival and restricting various biological processes that are intensively consuming energy such as DNA replication or protein translation. By definition, such adaptive responses are highly dynamic and must be tightly controlled by regulatory mechanisms that are distinct from those involved in stress responses that usually lead to cell demise. Numerous studies have already delineated the role of p53 in acute stress responses using various experimental models, but much less is known about p53 functions during short-term adaptive responses. It is important to note that the majority of our experimental models, in particular those used *in vitro*, do not faithfully mimic physiological situations faced by normal cells, and are not adapted to precisely evaluate p53 activities during adaptive responses. Finally, it is tempting to speculate that the multiple feedback loops in which p53 is involved define a finely tuned network that maintains p53 functions within a range of activity that is compatible with cell survival (See Figure 3). We propose that the genes contributing to the numerous feedback loops in which p53 plays a central role collectively define a genetic buffer that is instrumental to ensure energy and redox homeostasis. Perturbations of this network might lead to human diseases including cancer as well as some of the metabolic disorders that have been highlighted in this review. Given the worldwide increased prevalence of metabolic syndrome and its associated consequences, pharmacological manipulation of the p53 pathway appears as a promising strategy to improve the health of patients with such symptoms. However, we still need to improve our understanding of p53-associated metabolic networks in order to avoid harmful side effects of such strategies that could influence tumor incidence. This is particularly true for chronic diseases, such as type 2 diabetes or liver disease, which require long-term treatment.

AUTHORS' CONTRIBUTIONS

LLC, RR, LKL, GA, ML wrote the manuscript. LLC and ML prepared the figures.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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